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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/768,953	01/29/2004	Amedeo Leonardi	20199/100M275-US1	4561

7278 7590 01/24/2007

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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/768,953	LEONARDI ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *9,10,21-27,31-40 and 43-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-20,28-30,41 and 42* is/are rejected.

7)☒ Claim(s) *3-6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *14 June 2004 & 14 April 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-58 are presented for examination.

Acknowledgement is made of Applicant's claim for priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No. 60/506,631, filed September 26, 2003, and under 35 U.S.C. 119(a-d) to Italian Patent Application No. MI2003A-000151, filed January 30, 2003, of which a certified copy was received March 2, 2006 and placed of record in the application.

Applicant's Information Disclosure Statements (IDS) filed June 14, 2004 (three pages) and April 14, 2005 (one page) have each been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08a/b (four pages total), the Examiner has considered the cited references.

Applicant's response filed March 2, 2006 to the requirement for restriction/election dated January 12, 2006 was received and entered into the present application. However, the requirement for restriction/election of January 12, 2006 was vacated in view of the new requirement for restriction/election dated August 18, 2006. The requirement for restriction/election dated August 18, 2006 was modified via telephone during a conversation between Applicant's representative, Mitchell Bernstein, and Examiner Dwayne C. Jones. Applicant's response to this requirement for restriction/election filed October 27, 2006 has been received and entered into the present application.

Requirement for Restriction/Election

During a telephone conversation between Applicant's representative, Mitchell Bernstein, and Examiner Dwayne C. Jones, the requirement for restriction/election dated August 18, 2006 was herein modified to require restriction between the following groups of patentably distinct and/or independent inventions:

Group I, claims 19-20, directed to methods for treating neuromuscular dysfunction using a mGlu5 receptor antagonist in combination with an antimuscarinic agent, classified in class 514, subclass 277, for example, depending on the agents used.

Group II, claims 21-22, directed to methods for treating neuromuscular dysfunction using a mGlu5 subtype receptor antagonist in combination with an alpha-1-adrenergic antagonist, classified in class 514, subclass 277, for example, depending on the agents used.

Group III, claim 23, directed to methods for treating neuromuscular dysfunction using a mGlu5 subtype receptor antagonist in combination with a COX-2 inhibitor, classified in class 514, subclass 277, for example, depending on the agents used.

Group IV, claims 24-25, directed to methods for treating neuromuscular dysfunction using a mGlu5 subtype receptor antagonist in combination with a selective COX-1/COX-2 inhibitor, classified in class 514, subclass 277, for example, depending on the agents used.

Group V, claims 26-27, directed to methods for treating neuromuscular dysfunction using a mGlu5 subtype receptor antagonist in combination with a non-selective COX-1/COX-2 inhibitor, classified in class 514, subclass 277, for example, depending on the agents used.

Group VI, claims 50-58, directed to methods of identifying a compound useful for treating neuromuscular dysfunction of the lower urinary tract, classified in class 435, subclass 7.1, for example.

Claims 1-28 and 28-49 were identified as claims that link Inventions I-V.

Applicant was further required to elect a single species of mGlu5 subtype receptor antagonist, a single species of additional agent (e.g., antimuscarinic, alpha-1-adrenergic antagonist, etc.), and a single species of neuromuscular dysfunction for examination on the merits.

Applicant's election **without traverse** of the invention of Group I, directed to methods for treating neuromuscular dysfunction using a mGlu5 subtype receptor antagonist in combination with an antimuscarinic agent, and the further election **without traverse** of the species of MTEP, also known as 3-(2-methylthiazol-4-yl)-ethynylpyridine, as the mGlu5 subtype receptor antagonist; tolterodine as the antimuscarinic agent; and urinary incontinence as the neuromuscular dysfunction, in the reply filed October 27, 2006, is acknowledged by the Examiner.

Therefore, for the reasons above and those made of record at pages 2-8 of the previous Office

Action dated August 18, 2006, the election requirement is deemed proper and is made **FINAL**.

Claims 9-10, 21-27, 31-40 and 43-58 are **withdrawn** from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to non-elected inventions.

The claims corresponding to the elected subject matter are claims 1-8, 11-20, 28-30 and 41-42 and such claims are herein acted on the merits.

Objections to the Claims

Claims 3-6 are objected to because the word "selectivity" is misspelled at line 2 of each claim.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 11-20, 28-30 and 41-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 1 is directed to a method for treating neuromuscular dysfunction of the lower urinary tract in a mammal in need of such treatment comprising administering to said mammal an effective amount of a compound having selective affinity for the mGlu5 subtype of the metabotropic glutamate receptors.

In particular, the recitation of the administration of an effective amount of a compound having selective affinity for the mGlu5 subtype of the metabotropic glutamate receptors as stated in, for example, present claim 1, fails to delineate the function of the effective amount. It is necessarily implied from the present claims as written that the amount to be administered is intended for use to elicit a therapeutic effect. However, it is not clear as to what condition(s), disease(s) or disorder(s) of the host upon which

said amount is capable of exerting a therapeutic effect. Applicant's failure to define for what the amount is therapeutically effective renders the claim vague and indefinite.

For these reasons, the metes and bounds of the present claims cannot be identified and one of ordinary skill in the art would not necessarily be reasonably apprised of the scope of the claims. In light of such, claims 1-8, 11-20, 28-30 and 41-42 fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 11-20, 28-30 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cosford et al. (WO 2001/16121, 2001; cited by Applicant) in view of Bonney et al. ("Bladder Dysfunction in Schizophrenia", *Schizophrenia Research*, 25(1997):243-249) and Nilvebrant ("Clinical Experiences with Tolterodine", *Life Sciences*, 68(2001):2549-2556; cited by Applicant).

Cosford et al. teach compounds of the formula A-L-B, defined at pages 19-20, of which the species 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (Example 169, page 100) is expressly exemplified and is identical to Applicant's elected species of "MTEP" (see present claim 42), useful for therapeutic applications, such as, e.g., the treatment of schizophrenia (page 21, lines 1-9), comprising the administration of a therapeutically effective amount of at least one of the disclosed heterocyclic compounds to a patient having a disease (page 22, lines 26-29). Cosford et al. further teach that the disclosed compositions may be administered to a patient using oral, sublingual, intravenous, subcutaneous, transcutaneous, intramuscular, intracutaneous, intrathecal, epidural, intraocular, intracranial, inhalation, rectal or vaginal methods (page 23, lines 14-17) and may further be compounded with non-toxic, pharmaceutically acceptable carriers (page 23, lines 19-22), such as, but not limited to, sterile water, sterile saline, propylene glycols, polyethylene glycols, vegetable oils, etc. (page 24, lines 4-15). Cosford et al. additionally discloses dosage amounts typically in the range of about 0.001-100 mg/kg/day (page 25, lines 19-21), but further teaches that the specific therapeutically effective dose level for a particular patient will depend upon a variety of factors, e.g., the disorder being treated, severity of disease, age, sex, etc. (page 25, lines 11-19).

Here, though Cosford et al. teaches 0.001-100 mg/kg/day dose level and not a total daily dose, it would have been obvious that for an average 70 kg adult human, such a dose range would constitute daily dosage amounts of 0.07-7000 mg/day, which overlaps the dosage amounts presently claimed in present claims 16-18. In light of such, it is clear that the art recognized the administration of the claimed compound in amounts encompassing or overlapping those amounts presently claimed and, thus, the use of such a compound in amounts such as those presently claimed would have naturally commended themselves, and would have been *prima facie* obvious, to one of ordinary skill in the art. In addition, the concentration of the active ingredient is a result-effective variable, i.e., a variable that achieves a recognized result, and, therefore, the determination of the optimum of workable dosage range would be

well within the practice of routine experimentation by the skilled artisan, absent factual evidence to the contrary, and, further, absent any evidence demonstrating a patentable difference between the compositions used and the criticality of the amount(s).

Further, Cosford et al. meets each and every structural and physical limitation of the presently claimed species of 3-[(2-methyl-thiazol-4-yl)ethynyl]pyridine. Accordingly, the receptor selectivity and binding affinity properties of the compound that Applicant presently claims (i.e., at least about 10-fold, 25-fold, 50-fold, 100-fold or 500-fold selectivity for the mGlu5 subtype of metabotropic glutamate receptors or is a selective mGlu5 receptor antagonist; claims 2-7) are inherently present in the compound, whether recognized by the patentee or not. As taught by the MPEP, products of identical composition cannot have mutually exclusive properties. Please reference MPEP §2112.01.

Bonney et al. teaches that studies of schizophrenic patients have demonstrated particular anatomical lesions, such as ventricular enlargement (hydrocephalus), selective neuronal loss with gliosis and dopamine dysregulation that have been proposed to interrupt the pathway of bladder control or cause neurotransmitter dysfunction (paragraph bridging pages 243-244). Bonney et al. teaches that many schizophrenic patients have brain abnormalities that are similar to those associated with urge incontinence and detrusor hyperreflexia in neurological patients and proposes that bladder dysfunction and incontinence are neurobiological correlates of schizophrenia (abstract). Bonney et al. further discloses that incontinence was clearly associated with a diagnosis of schizophrenia, as evidenced by the percentage of schizophrenic patients with incontinence (i.e., 37%, see page 246, Table 2) versus patients with other mood disorders (i.e., 18%, see page 246, Table 2).

In view of such teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the disclosed compound(s) of Cosford et al. would have been reasonably expected to exert the same or substantially similar efficacy in the treatment of urinary incontinence because: (1) the compound(s) of Cosford et al. were known to have efficacy in treating

schizophrenic patients, (2) a significant proportion of schizophrenic patients also experience concomitant urinary urge incontinence as taught by Bonney et al., and (3) the urinary incontinence commonly seen in schizophrenic patients is considered to be correlated to and, i.e., result from, the brain abnormalities that are characteristic of schizophrenia, as also taught by Bonney et al. The skilled artisan would have been motivated to administer the compound 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine of Cosford et al. with the reasonable expectation of success in treating urinary incontinence in light of the fact that such a compound was known to have efficacy in the treatment of schizophrenia and, given the relationship between schizophrenia and urinary incontinence as discussed by Bonney et al., one of skill in the art would have reasonably expected the same or substantially similar efficacy in treating urinary incontinence due to the neurobiological and pathophysiological similarities between the two conditions.

Further, Nilvebrandt teaches tolterodine as a non-selective muscarinic receptor antagonist for the treatment of overactive bladder that has a greater effect on the bladder than on the salivary glands *in vivo*, which improves the tolerability of the compound by decreasing the incidence of dry mouth (abstract). Nilvebrandt further teaches that the efficacy of tolterodine in treating overactive bladder is equal to that of oxybutynin, but with significantly enhanced tolerability (abstract). Nilvebrandt quantifies the activity of tolterodine versus oxybutynin in treating episodes of urinary incontinence at Figure 2(A), which shows tolterodine to have substantially similar inhibitory activity to that of oxybutynin (page 2552).

One of ordinary skill in the art would have been motivated to combine the pharmaceutical composition of Cosford et al. with the muscarinic receptor antagonist tolterodine as taught by Nilvebrandt because each was known or recognized in the art to be useful for the same therapeutic purpose of treating urinary incontinence. The very fact that each was known in the prior art to have the same therapeutic utility raises the reasonable expectation of success that the two compositions, when combined, would have, at minimum, additive, if not synergistic, incontinence-ameliorating effects when combined.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is

prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

Conclusion

Rejection of claims 1-8, 11-20, 28-30 and 41-42 is proper.

Claims 9-10, 21-27, 31-40 and 43-58 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Leslie A. Royds
Patent Examiner
Art Unit 1614

January 16, 2007

Ardin H. Marschel 1/17/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER